PATENT SPECIFICATION

NO DRAWINGS

Inventors: WILLIAM ROBERT WRAGG and ANTHONY STANLEY FENTON ASH

839,628

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International Classification:—C07d.

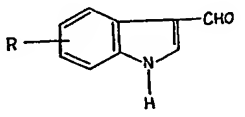
COMPLETE SPECIFICATION

Improvements in or relating to Indole Derivatives

We, MAY & BAKER LIMITED, a British Company, of Dagenham, in the County of Essex, England, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is for improvements in or relating to indole derivatives and has for its object the provision of new indole derivatives useful as intermediates in the preparation of therapeutically active compounds.

The new indole derivatives provided by the present invention are the indole - 3 - aldehydes of the formula:



I

wherein R represents an aralkoxy (preferably benzyloxy) group preferably in the 5 - position.

The novel compounds of the present invention are of importance primarily as intermediates in the preparation of 3 - aminoalkylindoles into which they may be converted by condensation with a nitroalkane, followed by reduction of the nitro group and the double bond of the 3 - nitroalkenylindole thus formed and, if desired, conversion of the aralkoxy group into a hydroxy group. Preferably the nitroalkane contains a straight- or branched-chain alkyl group containing from 1 to 5 carbon atoms.

The 3 - aminoalkylindoles which may thus be prepared and which include 3 - 2^1 - aminoethyl - 5 - hydroxyindole (5 - hydroxytryptamine), otherwise known as serotonin, and its analogues such as 3 - 2^1 - aminopropyl - 5 - hydroxyindole, possess valuable pharmacological properties, having, for example, haemostatic activity or being effective in the regulation of vascular tone and blood pressure or of kidney activity, or in the restoration or maintenance of normal mental activity.

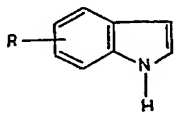
5 - Benzyloxyindole - 3 - aldehyde is a particularly valuable intermediate for the preparation of serotonin and its 3 - 2^1 - aminopropyl homologue. It may be converted to the latter as follows:

1) Conversion into 5 - benzyloxy - 3 - 2^1 - nitroprop - 1^1 - enylindol by treatment with nitroethane in the presence of an alkaline catalyst such as benzylamine.

2) Reduction to the 3 - 2^1 - aminopropyl compound, for example using lithium aluminium hydride.

3) Removal of the benzyl group by hydrogenation to give the corresponding 5 - hydroxy compound.

According to a feature of the present invention the new compounds may be prepared by reaction of an indole compound of the general formula:



II

wherein R is as hereinbefore defined, e.g. 5 - benzyloxyindole (prepared according to the method of BOEHME, JACS, 75, 2502, (1953)), with an NN - dihydrocarbon - substituted formamide, preferably dimethylformamide, in the presence of a condensing agent, preferably phosphorus oxychloride, followed by alkaline hydrolysis of the product obtained to the corresponding indole - 3 - aldehyde.

The invention is illustrated by the following Examples:

EXAMPLE I

Phosphorus oxychloride (66.8 g.) was added

[*Price 3s. 6d.*]

dropwise with stirring to dimethylformamide (116 g.) in a flask protected from atmospheric moisture at 10—20° C. 5 - Benzyloxyindole (98 g.) in dimethylformamide (69.5 g.) was then added slowly with stirring at 15—25° C. after which the mixture was held at 35° C. (±2°) for 45 minutes and poured on to crushed ice. The solid which separated was filtered off, washed with ice-water and hydrolysed by boiling for 2 minutes with *N* sodium carbonate (500 cc.). The resulting suspension was cooled in ice and the solid filtered off and washed successively with water (1750 cc.), ice cold methanol (200 cc.) and ether (750 cc.). After recrystallisation from a mixture of dimethylformamide (400 cc.) and water (100 cc.), the resulting 5 - benzyloxyindole - 3 - aldehyde had melting point 239—241° C.

Examples II to IV illustrate the conversion of the product of Example I into the 3 - 2^1 - aminopropyl homologue of serotonin by the methods hereinbefore described.

Example II

5 - Benzyloxyindole - 3 - aldehyde (65 g.) was prepared as in Example I, dissolved in redistilled nitroethane (1920 cc.) containing benzylamine (5.52 g.) as catalyst and refluxed for one hour. The solid which separated on cooling was filtered off, and washed with ether. Further material was obtained by evaporating the filtrate to dryness under reduced pressure. Recrystallisation from ethyl alcohol (4.2 l.) gave 5 - benzyloxy - 3 - 2^1 - nitroprop - 1^1 - enylindole, m.p. 194—196° C.

Example III

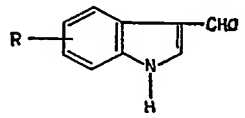
5 - Benzyloxy - 3 - 2^1 - nitroprop - 1^1 - enylindole (7.7 g.) was prepared as in Example II, dissolved in dry tetrahydrofuran (90 cc.) and added with stirring to a suspension of lithium aluminium hydride (3 g.) in boiling tetrahydrofuran (100 cc.). The mixture was refluxed overnight, cooled and excess lithium aluminium hydride decomposed by addition of wet ether (50 cc.) and water (5 cc.). The complex was decomposed by stirring with 50% sodium hydroxide solution (25 cc.) and the mixture filtered through the diatomaceous earth known as "Hyflo Supercel" ("Hyflo" and "Supercel" are Registered Trade Marks). After washing the residue on the filter with ether (4×25 cc.), the organic layer in the filtrate was separated, washed with water (3×50 cc.) and basic material was extracted with 2*N* acetic acid (2×50 cc.). The acid extract was made strongly alkaline with 2*N* sodium hydroxide and the organic base was extracted with ether (100, 50 and 25 cc.). The combined ether extracts were washed with water (5×30 cc.), dried over sodium sulphate and then evaporated under reduced pressure. The oily product was triturated with *N* sulphuric acid and the resulting solid filtered off, washed with acetone and dried. After recrystallisation by addition of ether (450 cc.) to a solution in methyl alcohol (50 cc.) the 5 - benzyloxy - 3 - 2^1 - aminopropylindole sulphate monohydrate melted at 146—148° C. (dec.) in a sealed evacuated tube.

Example IV

Palladium chloride (0.04 g.) and acid-washed charcoal (0.2 g.) were suspended in water (12 cc.) and hydrogenated at room temperature and atmospheric pressure until no further hydrogen was taken up. A suspension in ethyl alcohol (18 cc.) of 5 - benzyloxy - 3 - 2^1 - aminopropylindole sulphate monohydrate (1 g.), prepared as in Example III, was added and the resulting suspension hydrogenated under similar conditions. The catalyst and charcoal were filtered off through "Hyflo Supercel" and the filtrate evaporated under reduced pressure in an atmosphere of hydrogen, leaving 5 - hydroxy - 3 - 2^1 - aminopropylindole sulphate monohydrate as a friable pale-pink hygroscopic glass, m.p. 130—133° C. in a sealed evacuated tube.

WHAT WE CLAIM IS:—

1. Indole - 3 - aldehydes of the formula:

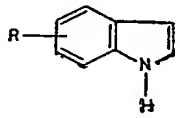


wherein R represents an aralkoxy group.

2. Indole - 3 - aldehydes as claimed in claim 1 wherein R represents a benzyloxy group.

3. 5 - Benzyloxyindole - 3 - aldehyde.

4. A process for the preparation of an indole - 3 - aldehyde as specified in any one of the preceding claims which comprises the reaction of an indole compound of the general formula:



(wherein R represents an aralkoxy group) with an NN - dihydrocarbon - substituted formamide in the presence of a condensing agent followed by alkaline hydrolysis of the resulting product to the corresponding indole - 3 - aldehyde.

5. A process as claimed in claim 4 wherein said indole compound is 5 - benzyloxyindole.

6. A process as claimed in claim 4 or 5 wherein the substituted formamide is dimethylformamide.

7. A process as claimed in claim 4, 5 or 6

wherein the condensing agent is phosphorus oxychloride.

8. A process as claimed in claim 4 when carried out substantially as described in the foregoing Example I.

J. A. KEMP & CO.,
Chartered Patent Agents,
9 Staple Inn, London, W.C.1.

PROVISIONAL SPECIFICATION

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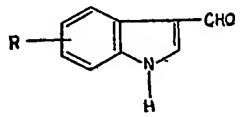

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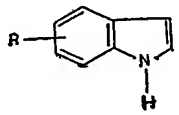
2) Reduction to the 3 - 2^1 - aminopropyl compound, for example using lithium aluminium hydride.

3) Removal of the benzyl group by hydrogenation to give the corresponding 5 - hydroxy compound. If desired the resulting 3 - 2^1 - aminopropyl - 5 - hydroxyindole may be converted into its double salt with creatinine sulphate.

According to a feature of the present invention the new compounds may be prepared by reaction of an indole compound of the general formula II:



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EXAMPLE IV

Palladium chloride (0.04 g.) and acid-washed charcoal (0.2 g.) were suspended in water (12 c.c.) and hydrogenated at room temperature and atmospheric pressure until no further hydrogen was taken up. A suspension in ethyl alcohol (18 c.c.) of 5 - benzyloxy - 3 - 2^1 - aminopropylindole sulphate monohydrate (1 g.), prepared as in Example III, was added and the resulting suspension hydrogenated under similar conditions. The catalyst and charcoal were filtered off through "Hyflo Supercel" and the filtrate evaporated under reduced pressure in an atmosphere of hydrogen. The syrup obtained was dissolved in a solution of creatinine sulphate hemihydrate (0.5 g.) in hot water (2.9 c.c.). Hot acetone (21 c.c.) was added with stirring and the solid which separated was filtered off and washed with acetone. The product was recrystallised by dissolving in hot water (2 c.c.) and adding ethyl alcohol (9.5 c.c.) to yield 5 - hydroxy - 3 - 2^1 - aminopropylindole creatinine sulphate m.p. 150—152° C. (dec.) in a sealed evacuated tube.

For the Applicants,
J. A. KEMP & CO.,
Chartered Patent Agents,
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